Current challenges in travelers' malaria

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INVITED COMMENTARY

Current Challenges in Travelers' Malaria

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Abstract Travel health providers are often confronted with complex scenarios when advising travelers on malaria prevention. Current challenges in prevention include malaria risk assessment, where a detailed itinerary and knowledge of malaria epidemiology are needed. Up-to-date information on the correct use, limitations, and drug interactions of current priority chemoprophylaxis agents (atovaquone/proguanil, mefloquine, doxycycline) is key. Another challenge is to identify and reach travelers who are most at risk of malaria, such as the traveler visiting friends and relatives. Posttravel, delays in presentation, diagnosis, and inappropriate treatment of malaria are key risk factors leading to death. Treatment of malaria is an emergency requiring expert in-patient management and referral to a center with adequate expertise. Artemisinin combination therapies are the drugs of choice for uncomplicated malaria. Complicated malaria is treated preferably with intravenous artesunate, and the supply and quality of this life-saving antimalarial in some settings can pose one of the most urgent challenges in travelers' malaria.

Keywords Malaria · Traveler · Chemoprophylaxis · Atovaquone/proguanil · Mefloquine · Doxycycline · ACT · Artesunate · Treatment · Interactions

Introduction

The prevention and treatment of malaria in travelers pose important challenges in travel medicine. World Tourism Organisation data suggest that there are approximately 180 million arrivals in malaria-endemic areas each year and that the numbers are increasing with particular growth (+7 %) in travel to sub-Saharan Africa, an area highly endemic for malaria [41].

Malaria remains the most important, acute, and potentially life-threatening tropical disease encountered by Western travelers, as shown in a recent GeoSentinel multicenter study where 76.9 % of returning travelers who presented with a potentially fatal, travel-acquired illness were diagnosed with *Plasmodium falciparum* malaria [1]. Travel health providers are often confronted with complex scenarios when advising travelers on malaria prevention. This article highlights the most important current challenges.

Risk Rating

A major issue for travel health practitioners is malaria risk assessment. Even the global risk of malaria in endemic areas is hard to quantify, but recent data suggest that there are 250 million clinical cases per year, with about 800,000 deaths [42]. Areas at highest risk are in Africa and Southeast Asia, but even within high-risk countries, many typical tourist destinations are malaria free (Fig. 1, Malaria Map), so simply labeling a country as "malaria endemic" will not provide enough detail for risk assessment. For example, a traveler to Thailand, officially a malaria-endemic country with some high-risk areas, may visit only malaria-free areas such as Bangkok, Phuket, or Ko Samui, and this individual will not need malaria prevention measures. Several facets need to be included in this risk analysis. The key question is, where is your traveler going? A detailed itinerary and knowledge of malaria epidemiology are needed. The intensity of malaria transmission at the destination is probably the most important variable in the risk analysis. Sub-Saharan Africa is considered a high-risk region, whereas Southeast Asia and Central America have less transmission (with some exceptions). To put this is in a numerical context based on imported malaria cases per 100,000 travelers, malaria risk will vary from very high risk in Central

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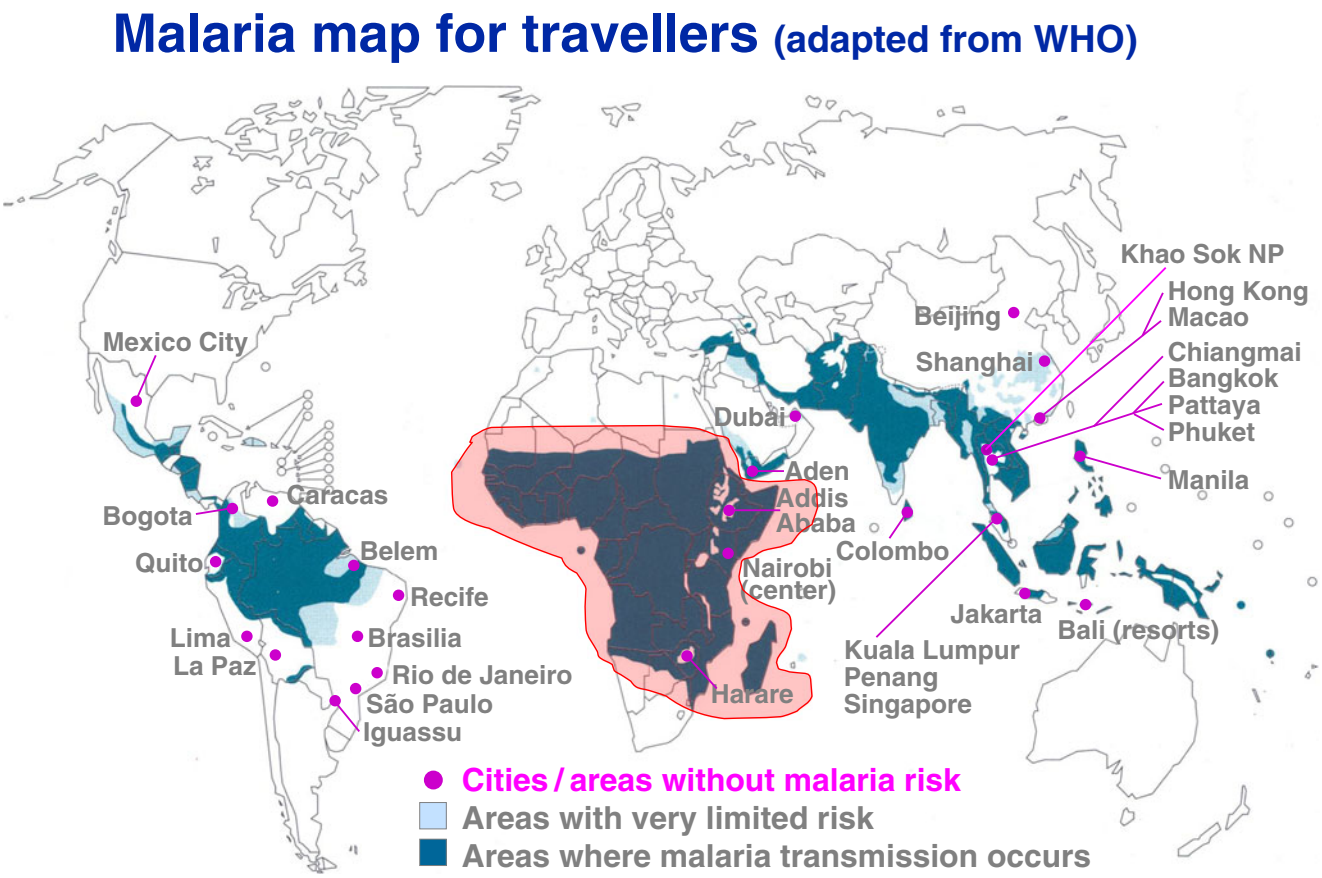

Fig. 1 Malaria map for travelers. (Adapted from WHO). Red shaded area indicates high risk African areas

Africa (estimated 357 cases per 100,000 travelers) to significantly lower risk in Central America (estimated 1.3 cases per 100,000 travelers) [2, 3].

The species of malaria at the destination is also important, and there is flux in malaria epidemiology. Most infections imported to Europe and North America are *Plasmodium falciparum* infections, and this species remains the biggest threat (in terms of mortality) [4], but it is increasingly recognized that the more widely distributed *Plasmodium vivax* is not benign and also causes significant morbidity and, sometimes, fatal disease in travelers [4, 5•, 6]. A recent paper examined the current failure of conventional malaria chemosuppression in preventing *P. vivax* malaria and called for a new look at primaquine causal prophylaxis to prevent both *falciparum* and *vivax* malaria [5•]. This is based on the knowledge that primaquine taken daily during exposure to malaria infection eliminates early developmental stages of the parasite in the liver cycle (Fig. 2). Primaquine should be prescribed only for G6PD-normal persons.

The "one health" concept is also important in travelers' malaria. The entry of a new malaria species, *Plasmodium knowlesi,* into the human population demonstrates a parasite crossing to man from nonhuman hosts, monkeys [6]. Globally speaking, the number of human infections with *knowlesi* is small, but certain foci are important sources of this malaria, and it is emerging as a risk for travelers to forested areas of Southeast Asia and should be taken into account in the risk assessment.

Traveler characteristics are also of vital importance in the risk assessment. Travelers' malaria has many faces and multiple facets, but those at highest risk of acquiring malaria are travelers of African heritage who visit friends and relatives (VFR) [3]. This poses a major challenge for travel health providers, since VFR travelers are less likely to seek advice prior to travel and may not be in a position to afford expensive antimalarials. New approaches, perhaps with an emphasis on primary health-care providers giving travel health advice, are urgently needed to target the VFR traveler.

In contrast to the high risk of acquiring malaria in the VFR group, the risk of dying from travelers' malaria is highest in business travelers and tourists, particularly the elderly, and in returned travelers who present to clinics or practitioners who have little or no experience in dealing with malaria [1, 3]. Men are more likely to acquire malaria and have more serious disease than women [7•]. Travelers to high-risk areas really need to be convinced of the need for effective malaria chemoprophylaxis medication and mosquito bite prevention.

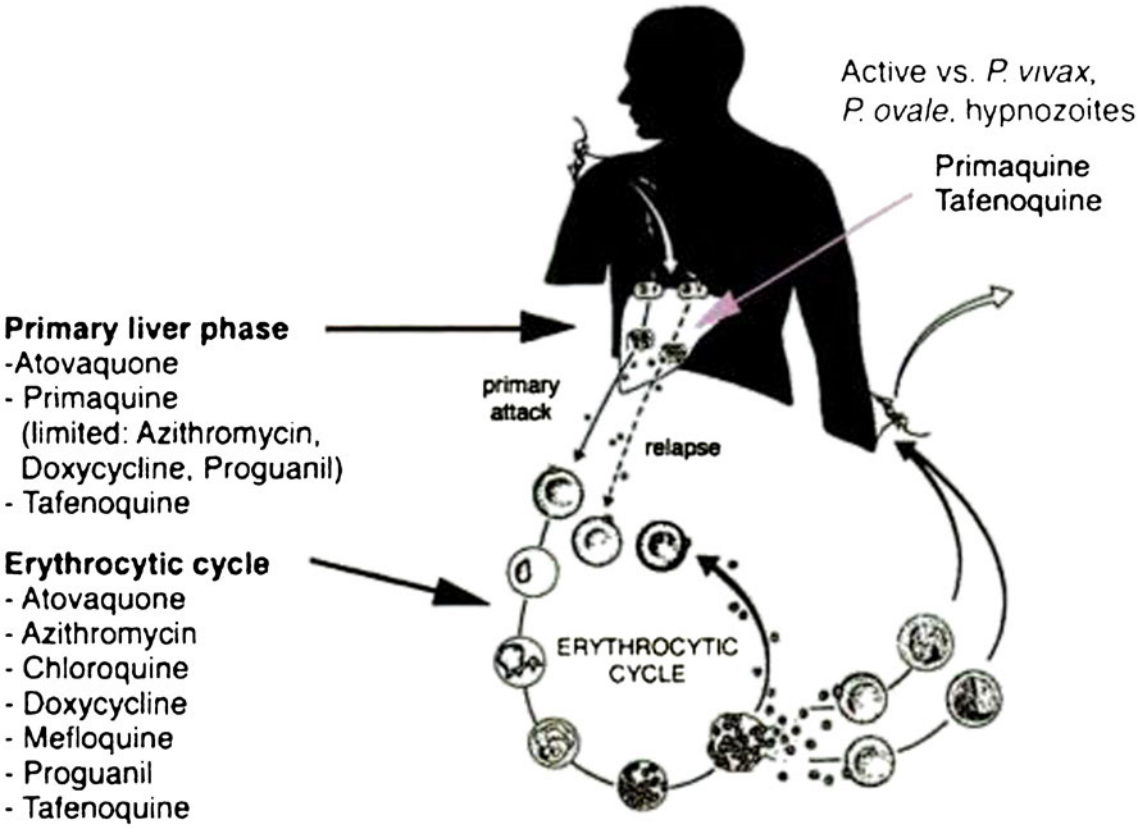

Fig. 2 Efficacy of anti-malarial drugs at various sites in the life cycle. (With permission from Schlagenhauf P, Funk M, PDQ Travelers' Malaria, BC Decker 2005)

Chemoprophylaxis Conundrums

The next challenge is to prescribe an appropriate chemoprophylaxis. Factors such as drug efficacy, tolerability [7•], price, and traveler characteristics will impact the choice. The current priority antimalaria chemoprophylctic regimens are atovaquone/proguanil, mefloquine, and doxycycline (Fig. 3). Current guidelines, such as the CDC malaria recommendations, should be consulted for correct use and dosages of antimalarial medication [43]. All the priority medication options are very effective against malaria, except in some foci of multidrug-resistant malaria in Thai border areas. Antimalarials are, however, associated with a high incidence of adverse events [7•, 8] and it is worthwhile to discuss fears, myths, and facts regarding these adverse events, since perception will impact traveler behavior and adherence to the chemoprophylaxis. Matching the traveler to the appropriate chemoprophylaxis can be complex, especially for small children [8], travelers with comorbidities, and the pregnant traveler. Atovaquone/proguanil paediatric tablets are a good choice for children (>11 kg in Europe, >5 kg in the U.S.) on short trips, or longer term if the budget allows. Mefloquine is a practical, cost-effective option for children (>5 kg) [8, 9•] who stay for longer periods in malaria-endemic areas, but parents need to disguise the bitter taste with chocolate or yoghurt. Doxycycline is less frequently used for children (>12 years) (Table 1).

Older travelers are widening their travel expectations, often despite comorbidities, and many questions arise when recommending chemoprophylaxis where the traveler is already taking several medications for routine conditions. A recent U.S. study of adults 57–85 years of age showed that 81 % are taking at least one prescription drug, 42 % are taking at least one OTC drug, and 49 % are using dietary supplements. The results of this study would suggest that 1 in 25 individuals are at risk for a major drug–drug interaction. A thorough check of traveler comorbidities and comedication is key. Some examples of important drug interactions are the following: Travelers on warfarin may need INR checks or a change of prophylaxis if using doxycycline or atovaquone/proguanil; mefloquine should not be started until after the traveler has completed taking his live oral typhoid fever vaccine. Tables 2, 3, and 4 show possible interactions that may occur with malaria chemoprophylaxis.

The pregnant traveler poses a special challenge in malaria chemoprophylaxis. Malaria during pregnancy poses a significant risk to the mother and foetus. Atovaquone/proguanil and doxycycline are currently not recommended in pregnancy, but mefloquine is an option, and a recent analysis has shown that

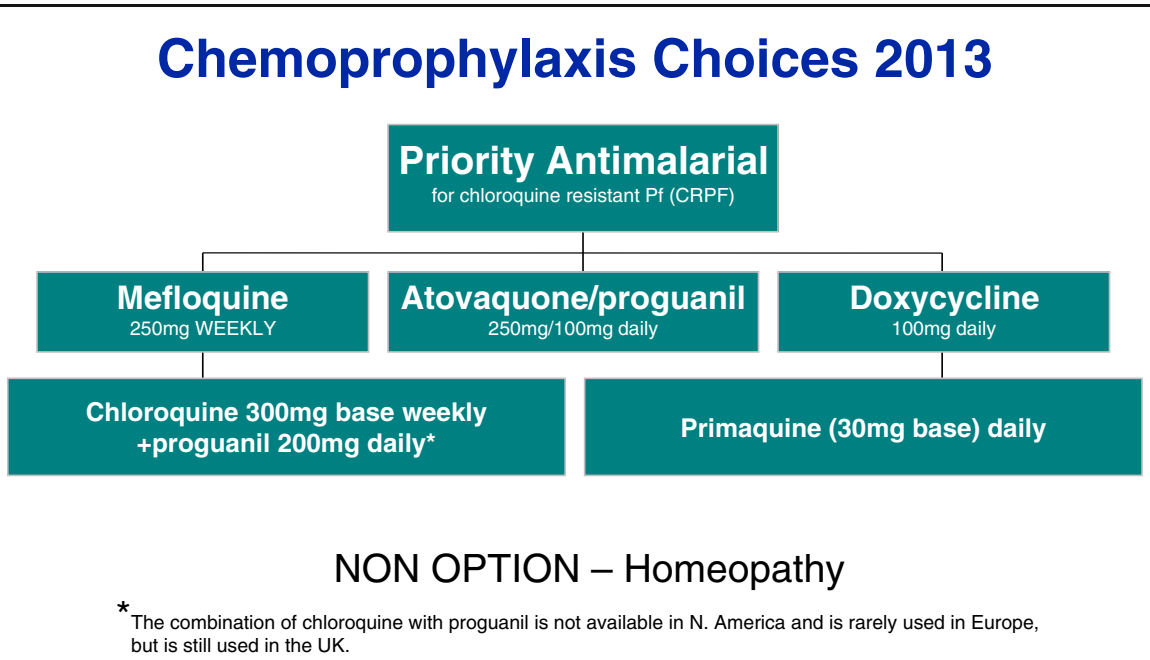

Fig. 3 Chemoprophylaxis choices (2013)

the birth prevalence of malformations (4.4 %) in mefloquine-exposed mothers is comparable to background levels [10••].

Personal Protection Problems

Travelers need concise information on antimosquito measures, and this preventive area is a real challenge. Surveys have shown that adherence to personal protection measures can be dismal. Remind the traveler of the simple fact: no bite, no malaria. The female malaria mosquito, *Anopheles*, bites at night. A combination of insect skin repellents (such as DEET, IR3535, Icaridin) (Table 5), (pyrethroid) insecticide-impregnated clothing, and bed nets/air conditioning is effective in malaria prevention, but adherence to these measures is poor, and time spent convincing the traveler is well invested. It is also worthwhile to explode the myths about measures that are ineffective, such as the use of garlic, perfume, vitamin B complex, and ultrasound devices.

Diagnostic Dilemmas

Diagnostic tests for malaria should be performed in any ill patient who has a history of exposure—that is, patients with a history of travel to malaria-endemic areas, whether or not they are febrile at presentation [12]. Health care facilities may not have the expertise to do a microscopic examination of thick and thin Giemsa stained blood films. If patients with a history of travel to malaria endemic areas and with fever can not have a reliable microscopy or RDT for malaria, they should be referred to the nearest center, where these facilities and skills are available. Microscopic examination of Giemsa-stained thin and thick blood films remains the gold standard because it is rapid,

Table 1 Antimalarial chemoprophylaxis for infants and small children

Anti-malarial	Chemoprophylaxis	Dosing	Comments
Atovaquone/proguanil	*>5 kg CDC >11 kg Europe, manufacturer	-Daily -Pediatric tablets	-Palatable -Expensive
Chloroquine	All ages and weights	5 mg base/kg Weekly	-Limited use due to resistance
Doxycycline	Children >12 years in Europe, > 8 years in U.S.	1.5 mg salt/kg Daily	Contraindicated for small children
Mefloquine	>5 kg	5 mg/kg Weekly	- Bitter taste - Weekly
Primaquine	Children >4 years WHO CDC specifies no lower age limit	0.5 mg/kg base Daily	-G6PD testing essential -Last choice

*new

Table 2 Possible interactions with mefloquine prophylaxis

Possible interaction with:	Risks	Consequence/Recomendation
Chloroquine	ECG alterations. Convulsions	Don‘t combine. Change to Doxy or At/P
Anticonvulsive drugs (e.g., carbamazepine, phenytoin etc.)	Reduced plasma concentration of anti-convulsant	Change prophylaxis to Doxy or At/P
Oral typhoid fever vaccine (Vivotif®)	Inactivation of vaccine due to mefloquine	Cannot be used concomitantly
Antihyperglycemics	Blood sugar levels may be affected	Control blood sugar levels
Cimetidine	May increase MQ plasma levels	Caution regarding increased risk of adverse events

easy to perform, and sensitive [13], with a sensitivity down to five parasites per microliter in expert hands. Thick blood films have higher sensitivity compared to thin blood films because a higher volume of blood is examined because the red blood cells are lysed. The thin blood film are used to assist species diagnosis. It is important to diagnose malaria early, when it is uncomplicated and only centers able to perform microscopy should manage patients with malaria. After treatment has been initiated a reduction in parasitemia may not be seen for another 24 hours. Rapid diagnostic tests including a pan-plasmodia antigen can detect parasitmia as low as 200 parasites per microliter [11]. PCR is not used in routine diagnosis as it is not always available. However PCR is useful for confirmation of the species diagnosis and for cases with low parasitemia where microscopy may be doubtful and the rapid diagnostic tests negative.

RDTs are increasingly used in medical centers with limited access to experienced microscopists; but, a rapid test cannot determine the parasite density. False negative RDTs in patients with very high parasite densities have been described, probably due to the so-called “pro-zone” phenomenon [12, 13]. This problem seems to be limited to tests based on detection of circulating histidine-rich protein 2 (HRP2) [11]. Mutations in the HRP2 gene may result in false negative tests [14, 15]. Assays are available that detect all species—that is, *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*—on the basis of the detection of the panmalarial antigens aldolase and LDH [16]. *Plasmodium knowlesi* infections will be detected by rapid tests, which include the pan-plasmodial aldolase or LDH antigens [9•, 17].

The latest results of the World Health Organization (WHO) multicenter evaluation of different rapid diagnostic tests show that the best performance was found with tests based on a combination of the HRP2 and pan-plasmodial proteins [9•].

Clinicians using rapid tests need to be aware that no RDT test so far is 100 % reliable and that blood film examinations should be done in parallel. Because microscopy may be negative especially in non-immunes with a very low parasitemia, it is recommended that three blood films are examined with approximately 24 hours interval to make sure that patients presenting with low level parasitemia are not missed. If the suspicion of malaria remains after three negative samples, expert advice should be obtained from a tropical or infectious disease specialist. After diagnosis, daily blood films should be examined until they are negative for asexual parasites (i.e., rings, trophozoites, schizonts). Gametocytes do not multiply or cause clinical illness and may remain after clearance of the asexual parasitaemia.

Tricky Treatments

In the U.K., between 1987 and 2006, 25,054 patients notified with *Plasmodium falciparum*, of whom 184 died [2].

Table 3 Possible interactions with atovaquone/proguanil prophylaxis

Possible interactions with:	Risks	Consequences/Recommendation
Metoclopramide, rifampicin, rifabutin	Decrease serum concentration of atovaquone/proguanil	Change to mefloquine or doxycycline prophylaxis
Indinavir (HIV therapy)	Atovaquone decreases plasma level of indinavir by 23 %	Change to mefloquine or doxycycline prophylaxis
Warfarin*	Atovaquone may displace warfarin, leading to increased serum warfarin	Single report* – monitor INR
Paracetamol, benzodiazepines, aciclovir, opiates, cephalosporins, antidiarrheals, laxatives	Decrease the plasma concentration of atovaquone	Importance unclear – probably not crucial to change antimalarial
Oral typhoid fever vaccine (Vivotif®)	NO interaction	Can be used concomitantly

*Hidalgo et al. Ann Paharmacother 2011;45:e3 ** Faucher JF CID 200

Table 4 Possible interactions with doxycycline

Possible interaction with:	Risks	Consequences/Recommendations
Warfarin anticoagulants	Anticoagulant effect of warfarin is enhanced	Control prothrombin time (INR) or change prophylaxis
Antacids (with Mg, Ca, Al), laxatives, oral iron, antidiarrheals	Agents bind with doxcycline	Take 3 h after doxy
Carbamazepine. Barbiturates, phenytoin Glucose urinary tests	Decrease half-life of doxycycline	Change prophylaxis or dosage adjustment of doxy (2×)
Glucose urinary tests	May be false negative or positive	Control blood sugar
Oral typhoid fever vaccine	Vaccine effectiveness may be reduced	Complete prior to Doxy prophylaxis
Digoxin	Serum digoxin may be increased	Limited data – no reports of toxicity
Oral contraceptives	Decrease in contraceptive effect?	No solid evidence

*CYP3A4 inhibitor (moderate)

Delays in presentation, diagnosis, and appropriate treatment of malaria were key risk factors, leading to death. Treatment of malaria is an emergency and requires expert in-patient management and treatment with fast acting antimalarials. A recent position paper on the management of imported malaria in Europe discussed malaria diagnostics and treatment options and dilemmas [12, 31••].

Treatment should provide a rapid clinical and parasitological cure within 3 days. Oral artemisinin combination treatment (ACT) is the medication of choice for uncomplicated malaria, as recommended by the WHO (Table 6) [18, 19]. Artemether/lumefantrine (Riamet) and dihydroartemisinin/piperaquine (Euartesim) are the two ACT formulations licensed for use in Europe. Dihydroartemisinin/piperaquine is the first antimalarial drug to be registered by the European Medicines Agency. Artemether/lumefantrine is registered in the U.S. and is the most widely used ACT globally. This combination is well tolerated and highly efficacious in all endemic regions, except for *P. falciparum* infections acquired in Cambodia and the border regions of Thailand with Myanmar, where multidrug-resistant *P. falciparum* strains are highly prevalent.

Artemether/lumefantrine should be administered with fatty food to obtain optimal plasma drug concentrations [20]. Dihydroartemisinin/piperaquine, in contrast, should be taken fasting.

Atovaquone/proguanil (Malarone) can be used as a first-line treatment for uncomplicated malaria and needs to be administered with fatty food to increase bioavailability. Atovaquone/proguanil is relatively slow acting, with considerably longer parasite clearance times, as compared with ACT. Atovaquone/proguanil is the preferred treatment option for uncomplicated falciparum malaria from regions with artemisinin resistance (Cambodia, Thailand border regions).

Treatment of severe, complicated falciparum malaria: A parasite density of 2 % or more in nonimmune and 5 % or more in malaria-immune subjects is defined as severe. Severe malaria may also be caused by species other than *P. falciparum,* especially *P. knowlesi*. *Plasmodium vivax* can also be severe in nonimmunes [21]. Severe imported *P. falciparum* malaria is an emergency that may rapidly become fatal [22].Intravenous artesunate (IVA) has been shown to be superior to intravenous quinine (IVQ) in overall survival and is safer and simpler to administer [18, 23, 24]. A recent Cochrane review concluded that treatment with artesunate significantly reduced the risk of death in both adults (RR 0.61, 95 % confidence interval [CI] 0.50–0.75; 1,664 participants, five trials) and children (RR 0.76, 95 % CI 0.65–0.90; 5,765 participants, four trials) [25]. Intravenous artesunate must be started immediately after the confirmation of the diagnosis, and the patients should be transferred to the ICU for management.

A recent study reported haemolytic anaemia in 6 out of 25 patients treated with IVA for severe imported malaria diagnosed 14–31 days after the first dose of IVA [26]. A larger

Table 5 Repellents: Pros and cons

Repellent	Advantages	Disadvantages
DEET	Widely used and tested, effective 20 % DEET protects for >5 h*	May damage fabrics and plastics
Bayrepel® Picaridin KBR 3023	19.2 % preparation similar protection to DEET best against An gambiae** Less irritating than DEET	Interindividual variation
EBAAP IR3535	Mean protection 23 min* Good cosmetic properties	Variation in efficacy
PMD Eucalyptus citriodora	96%protection for up to 4 h Plant-based repellent Well tolerated	Interindividual variation with lemon eucalyptus
Natural Oils	"Bio" – high acceptance	(Very) short protection duration

Table 6 Treatment of uncomplicated falciparum malaria in adults. (Adapted from reference [31••])

Adult Patients	Drug	Dosage	Comment
First line	Artemether/Lumefantrine (Riamet™)	Twice daily for 3 days >35 kg: 4 tablets each 20 mg/120 mg for 6 doses (0–8–24–36–48–60 h)	Take with fatty food, reduced efficacy in Cambodia and border regions of Thailand
	Dihydroartemisinin/Piperaquine (Eurartesim™)°	Once daily for 3 days 36 bis <75 kg: 3 tablets each 320 mg/40 mg 75–100 kg: 4 tablets each 320 mg/40 mg	Administration without food, at least 3 h from any meal
	Atovaquone/Proguanil (Malarone™)	Once daily for 3 days >40 kg: 4 tablets à 250/100 mg	Administration with fatty food
Second line	Quinine*/Doxycycline	Thrice daily 10 mg/kg quinine plus daily 200 mg doxycycline for 7 days	Loose drug combination, off-label use
	Quinine*/Clindamycin	Thrice daily 10 mg/kg quinine plus twice daily 10 mg/kg clindamycin for 7 days	Loose drug combination, off-label use
	Mefloquine (Lariam™)**	Split total dose in 2–3 doses 6–8 h apart 45–60 kg: 5 tablets (3+2 tablets) >60 kg: 6 tablets (3+2+1 tablets)	Administration after food intake monotherapy, which is not suitable for regions with multidrug-resistant falciparum malaria (SE Asia)

Note. Artemether/lumefantrine has to be administered with fatty food to obtain optimal plasma drug concentrations. Dihydroartemisinin/piperaquine should be taken fasting.

*Quinine dose provided as quinine sulphate

**Mefloquine is rarely used for treatment due to increased incidence of adverse events at treatment dosage

study including 55 patients with severe malaria reported late onset haemolytic anaemia in 6 patients (9 %) between 7 and 31 days after start of IVA [27], and three more cases have been reported [28]. In a large French study of about 400 severe malaria patients treated with IVQ in the ICU, 28.5 % of them required red blood cell transfusion for marked anaemia [29]. Patients should be monitored for 4 weeks following IVA for haemolysis and leukopenia. It is unclear whether this condition can occur after treatment with artemether/lumefantrine, but a single case has been reported in the literature [30]. IVA should be completed with a full course of ACT, atovaquone/proguanil, or mefloquine.

The management and treatment of complicated malaria should be centralized, and the patient should be transferred to a center where intravenous artesunate, skills in microscopy. Detailed recommendations can be found in a recent position paper on management of imported malaria in Europe [31••].

Tricky Treatment of *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*

Plasmodium ovale and *P. malariae* generally remain sensitive to chloroquine in all endemic areas, despite reports of delayed parasite clearance time [32]. *Plasmodium vivax* sensitivity to chloroquine has declined steadily in Indonesia, Peru, and Oceania [19], and a paradigm shift is imminent, with opinion leaders beginning to call for a switch to ACT as the drug of choice in Indonesia, Peru, and Oceania. The use of artemether/lumefantrine has been suggested as a pragmatic choice in areas with chloroquine-resistant *P. vivax* [33].

Mefloquine (15 mg/kg body weight as a single dose) has been found to be highly effective against *P. vivax*, with a treatment success of 100 % [34]. Monotherapy with doxycycline (100 mg twice a day for 7 days) results in poor cure rates against *P. vivax* [35], but quinine is also effective against chloroquine-resistant *P. vivax*, but it is not an ideal treatment because of low tolerability and the possibility of early relapses [34]. The first-line treatment for *P. vivax* is chloroquine, with ACT as second line if the response to chloroquine is poor.

Plasmodium vivax and *P. ovale* infections, but not *P. malariae*, require treatment with primaquine for 14 days to eradicate liver hypnozoites (Fig. 2). Primaquine is contraindicated in patients with deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) [36]. *Plasmodium vivax* strains with reduced susceptibility to primaquine are found in southern regions of Oceania and Southeast Asia and require a higher dose of primaquine (up to 0.75 mg/kg/day, max 30 mg per day) for 14 days to prevent relapses [37]. Primaquine 30 mg per day in adults tested negative for G6PD deficiency should be standard treatment for adult patients with *P. vivax* and *P. ovale* after G6PD testing [38].

Primaquine should be administered concomitantly with a partner blood schizonticide.

Treatment of *P. knowlesi* is not standardized. A patient suspected of *P. knowlesi* infection should be referred for expert diagnosis and treatment. Uncomplicated *P. knowlesi* cases can be treated with ACT, chloroquine, quinine, or atovaquone/proguanil [39]. A recent study showed that ACT cleared parasites faster than did comparator antimalarials. In severe *P. knowlesi* cases, the use of IVA was associated with a lower case-fatality rate (17 % vs. 31 %) and lower median parasite clearance time (2 days vs. 4 days) than was IVQ [40].

Thus, uncomplicated *P. knowlesi* should be treated with chloroquine or an ACT drug, and complicated *P. knowlesi* with IVA.

Conclusions

The prevention and treatment of travelers malaria is highly challenging. The pretravel risk assessment is key to defining the type and intensity of malaria transmission at the destination and to prescribing appropriate antimalarials that are individually tailored. Special attention to individual characteristics is essential. Risk groups, such as pregnant women, expatriate travelers, small children, the elderly, and those on polymedication, need special attention.

The most important challenge for travel health advisers and, indeed, for returned travelers is simply to "think malaria" when there is a suggestive travel history and to act promptly in case of fever. Treatment of malaria is an emergency and requires expert in-patient management and treatment with fast-acting antimalarials. Delays in presentation and diagnosis and inappropriate treatment of malaria are key risk factors leading to death.

Compliance with Ethics Guidelines

Conflict of Interest Patricia Schlagenhauf and Eskild Peteresen declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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